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**Prevalence, predictive factors, and clinical course of
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healing following non-surgical root canal treatment: a
prospective study**

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Prevalence, predictive factors, and clinical course of persistent pain associated with teeth displaying periapical healing following non-surgical root canal treatment: a prospective study.

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Abstract

Aims To investigate the prevalence, pain catastrophizing and other predictive factors, and clinical course of persistent pain/discomfort associated with teeth displaying periapical healing following non-surgical root canal treatment (NSRCT).

Methodology One-hundred-ninety-eight patients (264 teeth) who had NSRCT were reviewed at 5-14 months, post-operatively. Teeth with persistent pain or discomfort, plus evidence of periapical healing were further monitored 0.5, 4 & 10 years later. Pain Catastrophizing Scale (PCS) and Short Form of the McGill Pain Questionnaire (SF-MPQ) were completed. Predictive factors were investigated using logistic regression models.

Results Twenty-four per cent (60/249) of teeth displaying periapical healing at first review, were associated with persistent pain, or discomfort. Fifty-five teeth *was associated with a* monitored 6-7 months later, showed reduction in pain (17/30) or discomfort (7/25). CBCT of eight teeth with persistent symptoms and complete periapical healing (by conventional radiographs) revealed distinct, small apical radiolucencies ($n = 3$) or root-apex fenestration through *Q* buccal plate ($n = 2$). History of chronic pain (headache, temporo-mandibular joint, masticatory muscle, neck, shoulder, or back pain) ($P = 0.005$), pre-operative pain ($P = 0.04$), responsive pulp ($P = 0.009$), tooth-crack ($P = 0.05$) and small periapical radiolucency ($P = 0.005$) were significant predictive factors. The PCS revealed 16 patients (22 teeth) ~~studied~~ were catastrophizers ($PCS \geq 30$) but this had no influence on post-treatment symptoms ($P = 0.5$).



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associated with

Conclusions Persistent pain or discomfort associated with teeth showing periapical healing at the first review after NSRCT, decreased in intensity in most cases over the following 6-months. Longer-term follow-up showed spontaneous improvement or symptom resolution in the majority of those with confirmed radiographic absence of periapical disease. Five predictive factors (history of chronic pain, teeth with responsive pulps, association with pain, diagnosis of tooth-crack before treatment, and diameter of pre-operative radiolucency) were identified.

For Peer Review

Introduction

Persistent pain after root canal treatment (surgical or non-surgical) is often taken to be due to persistent periapical disease (Ng *et al.* 2008, ~~Ng *et al.* 2011~~). However, ~~when such symptoms arise after root canal treatment in the absence of overt clinical or radiographic evidence of persistent periapical or dental disease, it may be~~ indicative of other causes. Such manifestation is the subject of this study and has an average frequency (~~pooled~~) of 5-17 % of cases (Polycarpou *et al.* 2005, Klasser *et al.* 2011, Vena *et al.* 2014, Nixdorf *et al.* 2016).

Significant predictive factors influencing the persistence of pain after root canal treatment include: presence of pre-operative tooth pain, particularly that lasting more than 3 months; a history of systemic chronic pain problems; previous painful dental treatment; and female sex (Polycarpou *et al.* 2005, Nixdorf *et al.* 2010). ~~Conversely, patients' optimism about the treatment procedure may profoundly reduce the risk of persistent pain (Nixdorf *et al.* 2016).~~ In addition, individuals classified as catastrophizers, tend to magnify or exaggerate the threat-value or seriousness of the pain (Sullivan *et al.* 2005). It could be hypothesized that "pain catastrophizing" may contribute to their likelihood of reporting persistent pain. It is contended that patients may possibly be affected by this to the extent that they respond poorly to treatment, regardless of its immune-microbial effectiveness (Sullivan *et al.* 2005, Mankovsky *et al.* 2012). Conversely, patients' optimism about the treatment procedure may profoundly reduce the risk of persistent pain (Nixdorf *et al.* 2016). ~~It could be hypothesized that "pain catastrophizing" may contribute to their likelihood of reporting persistent pain. It is contended that patients may possibly be affected by this to the extent that they respond poorly to treatment, regardless of its immune-microbial effectiveness (Sullivan *et al.* 2005, Mankovsky *et al.* 2012).~~

The intensity of persistent pain after root canal treatment has been reported to vary from mild to moderate, with average intensities of 1.5 ± 1.8 (based on 0-10 rating scale) 1.5 ± 1.8 (Nixdorf *et al.* 2016) over a 6-59 month post-treatment period (Nixdorf *et al.* 2016). Such low levels of persistent pain do not appear to have a large impact on those experiencing it (Nixdorf *et al.* 2016). Nevertheless, lack of insight about the cause of symptoms leads to anxiety that can be debilitating for some patients; a satisfactory and plausible explanation *alone* may suffice to resolve such anxieties and enable coping strategies (Pigg *et al.* 2013). Part of the key to resolving the diagnostic dilemma is to exclude the presence of persistent periapical disease with greater certainty. This requires the use of imaging techniques with better sensitivity, such as cone-beam computed tomography (CBCT) (Kanagasingam *et al.* 2017). The additional use of CBCT has been evaluated for its potential to differentiate "atypical odontalgia" from symptomatic apical periodontitis (Pigg *et al.* 2011). However, the periapical status of root canal treated teeth with chronic persistent pain has not been explored by CBCT in previous studies (Polycarpou *et al.* 2005, Klasser *et al.* 2011, Vena *et al.* 2014, Nixdorf *et al.* 2016); nor has the long-term clinical course of such persistent pain/discomfort been systematically analysed, to better inform decision-making on management options.

The three-fold aims of this study were to investigate the: (1) prevalence; (2) pain catastrophizing and other predictive factors; and (3) clinical course, of persistent pain or discomfort associated with teeth exhibiting evidence of periapical healing following non-surgical root canal treatment.

Materials and methods

Ethical approval, inclusion & exclusion criteria

This study was approved by the Joint Research & Ethics Committee of UCL Hospitals NHS Trust (Reference number 96/E195). Informed consent was obtained from all patients.

Patients who had primary (*de novo* / *first time*) or secondary (*retreatment*) non-surgical root canal treatment of a permanent tooth completed ~~by staff or postgraduate students~~ in the Department of Endodontology, Eastman Dental Hospital, University College London Hospital, London, UK, between 1st July 2006 and 30th November 2007, were included.

All patients fulfilling the ~~above~~ inclusion criteria were invited to attend the first follow-up appointment between 6 and 12 months following completion of root canal treatment. Patients who failed to attend the first review appointment, those who were less than sixteen years old by the first review appointment, or were unable to complete the relevant questionnaires, were excluded. Teeth associated with pre-operative advanced periodontal bone loss to the apical third were also excluded.

Teeth exhibiting symptoms (pain or discomfort), coupled with radiographic evidence of periapical healing at the first review appointment, were reviewed 6-7 months later. Those failing to attend were excluded from the second part of the analyses. Patients presenting with ~~root treated~~ teeth with persistent ~~pain or discomfort~~ symptoms, as well as complete periapical healing were further monitored at 4 and 10 years after treatment.

Sample size estimation

A minimum sample size of 200 patients/teeth with clinical and radiographic evidence of periapical healing (complete or incomplete reduction of periapical radiolucency at first review) was established based on a similar study (Polycarpou *et al.* 2005).

Polycarpou *et al.* (2005) included 103 patients ~~judged to have successfully with root-~~
~~treated teeth exhibiting based on periapical healing, as well as persistent pain status,~~
of which ~~in 20% had persistent pain.~~ The sample size of 200 ~~was deemed to should~~
provide sufficient power for inclusion of 4 explanatory variables in the same logistic
regression model, assuming 20% of ~~positive cases exhibited~~ (presence of
pain/discomforts/symptoms (Peduzzi *et al.* 1996).)

Follow-up clinical and radiographic examination

Follow-up assessments of patients were performed by two authors (RP & Y-LN),
consisting of updating medical history, routine history-taking, and clinical plus
periapical radiographic examination of the studied teeth. Extra-oral examination
included clinical examination of the face, head and neck (~~for asymmetry, and tender~~
~~points, along with auscultation and palpation of the temporomandibular joints and an~~
~~assessment of the range of mandibular movements~~). Intra-oral examination
included an assessment of the patients' occlusion and any interferences on the root-
~~treated teeth.~~ Clinical details recorded included: tenderness ~~to palpation~~ of the
adjacent soft tissues, presence/absence of a swelling, sinus tract, periodontal
probing depths, tenderness to pressure or percussion of the tooth, and integrity of
the restoration margin. Any signs or symptoms originating from adjacent teeth were
assessed and accounted for.

Following the assessment, the ~~clinician interviewed the patient~~ was interviewed to
complete a modified version of the Short Form of the McGill Pain Questionnaire (SF-
MPQ), and the Pain Catastrophizing Scale. Four additional pain descriptor terms
were added to the SF-MPQ: *tingling, numbness, sensitivity, and itching.*

Periapical radiographs were taken, attempting to reproducing as closely as possible,
~~e-~~ the angulation of the immediate post-operative radiographs. Rinn paralleling

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3 devices (Dentsply Limited, Weybridge, Surrey, UK) and Kodak F-speed double
4 radiographic films (Eastman Kodak Company, Rochester, NY, USA) were used and
5 manually processed.
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9 In addition, as part of the routine clinical care, those teeth associated with persistent
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11 symptoms pain/discomfort at the second review but showing evidence of complete
12 radiographic healing were consented and subjected to cone-beam computed
13 tomography (CBCT) scans to rule out post-treatment periapical disease as the origin
14 of symptoms. CBCT exposures were undertaken using the Veraview Epocs 3D
15 scanner (J. Morita manufacturing corporation, Kyoto, Japan). All doses were as low
16 as reasonably practical in compliance with Ionising Radiation (Medical exposure)
17 Regulations (IRMER 2000). The field of view was limited (4 × 4 cm) and
18 encompassed the target and adjacent teeth and their surrounding structures. The
19 optimum exposure time (High-resolution mode, 15.8s), tube current (3.5 to 4.5 mA),
20 energy/potential (90.0 Kv), and reconstruction resolution (voxel size 0.08 mm) were
21 used to acquire an image of adequate diagnostic quality. The zoom reconstruction
22 feature was also used on critical areas; CBCT data were re-sliced using 0.08 mm
23 slice intervals and 1.5 mm slice thickness.
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39 Viewing of periapical radiographs and CBCT

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41 The two observers (RP & YLN) were pre-calibrated using a selection of 12
42 radiographs, three in each radiographic healing category (Table 1 Complete healing,
43 incomplete healing, failure, or uncertain). One observer (RP) then examined all the
44 radiographs on two separate occasions on a standard Rinn fluorescent lightbox
45 (Dentsply Ltd), under 2.5× magnification using a Brynolf viewer (Brynolf, Trycare
46 limited, Bradford, UK), in a darkened room. One third (33%) of the radiographs were
47 independently examined by the second observer (YLN) under the same conditions to
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determine inter-observer agreement on periapical healing outcome. Disagreements on decisions were resolved to agreement through discussion. One observer (RP) independently recorded the pre-operative size of the periapical radiolucency, along with the apical extent of the root-filling in relation to the radiographic apex, and presence of any extruded sealer. In multi-rooted teeth, the root with the worst outcome (highest score) of each parameter was recorded for the tooth: periapical status (intact periodontal ligament space=0, reduction in lesion size but PDL not intact=1, lesion size remained the same or increased=2), apical extent of root filling (0-2 mm within the radiographic apex=0, > 2mm short of radiographic apex=1, extruded beyond the radiographic apex=2), and presence of sealer extrusion (absent = 0, presence=1). All CBCT images were reported on by a Consultant radiologist blinded to the study, and included any pathosis associated with the target and adjacent teeth, and their associated anatomical structures.

Data management and analysis

Statistical analyses were performed using a computer statistics package (SPSS 15.0 for Windows; SPSS Inc. Chicago, IL, USA, 2006). The Cohen's kappa coefficient was calculated to assess both inter- and intra-observer reliability in determination of radiographic healing outcome. Good agreement was taken as >0.8, substantial as 0.61-0.8, and moderate 0.4-0.6 (Petrie & Watson 1999).

The internal consistency of the SF-MPQ was evaluated using the Chronbach's α and was considered acceptable if α was 0.7 or higher (Tavakol & Dennick 2011).

Pain intensities were calculated based on four measures from the SF-MPQ: (1) Visual Analogue Scale score from 0-10 rating scale; (2) Sum of scores from evaluative (0-5) and VAS scales (0-10) of SF-MPQ; (3) Total score from the descriptor section of the SF-MPQ (score of 0-3 for each of the 19 descriptors); and

(4) Number of Words Chosen (NWC) (maximum 19). It was noted that two distinct types of symptoms (pain versus discomfort) were reported, pain or discomfort. The proportion of teeth associated with pain (SF-MPQ pain VAS score > 0) or discomfort (SF-MPQ pain VAS score = 0, plus individual descriptor score > 0) was therefore calculated for each periapical healing category. Changes in pain or discomfort experience were calculated based on changes in VAS scores, or total SF-MPQ scores between appointments, respectively while changes in discomfort were calculated based on total SF-MPQ scores in patients who had scored zero on the VAS.

~~Total scores on the Pain Catastrophizing Scale (PCS) for each patient; and the median scores for all the teeth and for a subset of teeth associated with complete or incomplete healing were calculated.~~

Bivariate associations of putative predictors with “symptoms” (pain or discomfort data pooled) at the first review appointment, was assessed~~used~~ for screening independent variables for possible inclusion in multi-variable logistic regression modelling. Those~~Independent~~ variables showing significant association with “symptoms” at the 10% ~~significance~~ level were included in the multi-variable regression modelling. The odds ratios (ORs) and 95% confidence intervals (CIs) for assessing the strength of association ~~between potential predictors and the outcome of interest, “symptoms”,~~ were estimated using the robust estimator for standard errors (Desai *et al.* 2013) to account for the clustering effect of multiple teeth nested within the same patient.

Results

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Of the inception cohort of 288 patients fulfilling the inclusion criteria, 198 patients (264 teeth) attended the first (5-14 month post-operative) review, representing a recall rate of 69%.

The intra-observer reliability in ~~determining~~ the periapical status at the first review was substantial (kappa coefficient = 0.8; 95% CI: 0.7, 0.8). The inter-observer agreement based on 33% of the teeth improved from the first (kappa coefficient = 0.6; 95% CI: 0.4, 0.7) to the second (kappa coefficient = 0.97; 95% CI: 0.9, 1.0) reading.

The SF-MPQ demonstrated high internal consistency for the ~~present~~ cohort (Cronbach's α = 0.880). The alpha-if-item-deleted statistics showed that removing individual descriptors led to a reduction in Cronbach's α , with the exception of the descriptor "itching" (the removal of which did not change the α value).

Frequency and clinical course of post-treatment symptoms

At the first review, 25% of teeth displaying complete or incomplete periapical healing (62/249) were associated with either pain (n=34; SF-MPQ pain VAS score > 0) or discomfort (n=28; SF-MPQ pain VAS score = 0, plus individual descriptor score > 0) (Table 21). The average "pain" intensity reported for the 34 teeth is presented in Table 32. The frequency distribution of descriptor choice at the first review is presented in Appendix I.

The second review assessed 55 teeth in 48 patients who had ~~showed~~ signs of periapical healing ~~with~~ plus persistent ~~symptoms~~ pain or discomfort at the first review. The clinical course of the pain or discomfort is detailed in figures 1 and 2. Of the 30 teeth reviewed further ~~(Figure 1)~~, the pain intensity had decreased or disappeared for the majority (n= 23, 77%) (Figure 1 – see *footnote). Of the 25 teeth associated with signs of periapical healing plus discomfort reviewed further ~~(Figure 2)~~, the

discomfort had decreased in intensity or disappeared in 80% (n=20), but had become worse or painful in 12% (n=3) (Figure 2 – see *footnote). All the teeth without pain-free teeth but displaying healing healing at the first review and had further follow-ups (1-4 year) (complete = (45/49 teeth;) or incomplete = (105/138), remained symptom-free at further 1-4 year follow-ups (1-4 year)(Table 1).

Of the 10 periapically “healed” teeth (in 10 patients) judged to be periapically “healed” but associated with persistent symptoms (pain/discomfort) at the second review, eight were subjected to CBCT scans in 2007/8. The CBCT scans revealed no obvious apical pathosis associated with 3 teeth (38%), small but distinct apical radiolucencies associated with 2 teeth (25%), and root apices “fenestrating” the buccal cortical plate in of 3 teeth (37.5%) “fenestrating” the buccal cortical plate, rendering radiographic diagnosis of the apical status impossible.

The characteristics of these patients are presented in appendix II. Nine out of the ten patients were contacted 10 years later in 2017, seven reported freedom from any symptoms (n=7), one reported a different sensation (n=1), and one reported persistent “discomfort” (n=1) associated with the root-treated tooth.

Influence of “catastrophizing” on post-treatment symptoms

The PCS scores (mean = 11.8; 95% CI: 10.3, 13.3) revealed that only 16 patients (22 teeth) to be were classified as catastrophizers (PCS \geq 30). Bivariate analysis showed revealed catastrophizing did not to have significant ($P = 0.5$) predictive value for post-treatment symptoms at the first review. The factor was therefore not analysed further.

Predictive factors for coincidence of periapically healed/healing teeth with and symptoms at the first review

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Single variable logistic regression models including data from teeth ~~with displaying~~
~~some degree of~~ periapical healing (n = 249) at the first review, revealed eight
potential predictive factors (Appendix III). Several potential predictive factors showed
significant correlation between them and could not be entered into the same model
simultaneously due to collinearity ~~Appendix III~~.

The final two multivariable logistic regression models (Table 3) revealed the odds for
~~teeth in patients with a history of chronic pain problems (head, temporo-mandibular~~
~~joint/muscle, neck, shoulder, or back pain)~~ to be associated with persistent tooth
symptoms was 3.5-fold higher than for ~~teeth in patients without no~~ such history (OR
= 3.5; 95% CI: 1.5, 8.4). Teeth with ~~pulps responsive pulps to pulp tests before~~
~~treatment were had~~ 5-fold higher odds of ~~more likely to be associated with~~ persistent
symptoms (OR = 5.2; 95% CI: 1.5, 18.1). Teeth ~~associated with~~ pre-operative pain
had 2.9 times higher risk odds of persistent symptoms (OR = 2.9; 95% CI: 1.1, 8.1).
With each millimetre increase in diameter of pre-operative radiolucency, the ~~risk~~
odds of persistent symptoms ~~were as~~ reduced by 13% (OR = 0.87; 95% CI: 0.78,
0.97). Presence of crack only retained its predictive value at the 10 % level.

Discussion

The ~~final~~ sample size (198 patients/264 teeth) and recall rate (69 %) of the present
~~study were~~ comparable to ~~similar previous studies, in which where samples sizes~~
ranged from 7 to 276 teeth (Vickers *et al.* 1998, Polycarpou *et al.* 2005, Nixdorf *et al.*
2010, Klasser *et al.* 2011). A ~~study on persistent pain study conducted in general~~
~~practices within a research network (Nixdorf et al. 2016)~~ had included a substantially
larger cohort (651 cases) but their pre-operative diagnostic data and post-treatment
periapical healing status were not presented ~~or analysed~~.

~~Inclusion of patients with Contribution of more than one treated tooth per patient may complicates and confounds the analyses without special statistical measures. The present study accounted for anythe clustering effect of multiple teeth within the same patient in the regression models. This approach allowed investigation of the effect of several associated factors including whether: multiple teeth received root canal treatment (OR = 1.3; 95% CI: 0.7, 2.6), multiple treated teeth were adjacent to each other (OR = 1.1; 95% CI: 0.5, 2.6), or in the same (OR = 0.8; 95% CI: 0.3, 2.2), or opposing (OR = 0.7; 95% CI: 0.2, 2.0) arches. Previous studies had resolved the problem by randomly selecting only one tooth per patient for analyses (Polycarpou *et al.* 2005, Vena *et al.* 2014, Nixdorf *et al.* 2015) but, T this approach may risks losinge valuable information, in the process. The present study accounted for the clustering effect of multiple tooth within the same patient in the regression models. This approach allowed investigation of the effect of several associated factors including whether: multiple tooth received root canal treatment (OR = 1.3; 95% CI: 0.7, 2.6), multiple treated tooth were adjacent to each other (OR = 1.1; 95% CI: 0.5, 2.6), or in the same (OR = 0.8; 95% CI: 0.3, 2.2), or opposing (OR = 0.7; 95% CI: 0.2, 2.0) arches.~~

The Short Form McGill Pain Questionnaire (SF-MPQ) was adopted with the addition of four additional terms: tingling, numbness, sensitivity and itching because it was surmised that these terms may help describe sensations common sensations during wound healing (Marbach 1978, Bates & Stewart 1991, Henderson *et al.* 2006). Addition of all except "itching" could be justified based on alpha-if-item-deleted statistics. -Symptoms of such as anaesthesia, pruritis or pain, associated with mature scarrings, have been attributed to increased densities of mediators, SP and CGRP in healing wounds (Henderson *et al.* 2006). The descriptor, "litching" was only selected

by only two patients but ~~the term~~ has been used by patients to describe pain ultimately diagnosed as "atypical odontalgia" (Marbach 1978, Bates & Stewart 1991). Twenty-nine patients specifically distinguished the experience of *discomfort* from *pain* associated with a root-treated tooth. This distinction, in the authors' experience, is often volunteered by patients and sometimes authoritatively corrected when an alternative ~~the other~~ term is used synonymously. The fact that patients independently make this distinction, made with such clarity and authority points to a potential biological difference that may have by patients seems to have been overlooked in the literature. Consequently, there is no validated questionnaire to measure "discomfort". The SF-MPQ incidentally did classify patients into those experiencing pain or discomfort and sought not to mix the two groups. Consistently, all patients experiencing *discomfort* scored zero on the VAS, but scored positively for selected descriptors on the SF-MPQ. The SF-MPQ may therefore be a suitable instrument for measuring discomfort but further formal validation is warranted. Nevertheless ~~However~~, the pain or discomfort data were pooled under "symptom" for analysis of predictive factors binary logistical regression due to as there was insufficient statistical power for multinomial regression to investigate whether the two types of symptoms had different sets of predictive factors.

The frequency of persistent tooth pain ~~teeth associated with pain~~ (14%) amongst the study cohort was more-or-less consistent with ~~the findings by~~ Nixdorf *et al.* (2016), who. They found that that 10% of their patients reported pain at 6 months post-operatively, regardless of periapical status. In the present study, the majority of teeth diagnosed with post-treatment periapical disease were asymptomatic (82%), in agreement with Polycarpou *et al.* (2005). Nixdorf *et al.* (2015) reported that ~~in their cohort, when~~ persistent tooth pain in 37% of the patients was attributed to

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3 symptomatic apical periodontitis (37%), but the source emanated from an adjacent
4 tooth in half of their cases. Such an association was not found in the present cohort;
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7 any symptoms originated from the adjacent teeth were excluded in the analyses.
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10 The persistence of symptoms long after technically adequate successful root canal
11 treatment may also be attributed to non-odontogenic problems (Nixdorf *et al.* 2015),
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13 such as Persistent Dentoalveolar Pain Disorder (PDAP) with no objective signs of
14 pathosis, also termed (or atypical facial neuralgia, or atypical odontalgia) (Marbach
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17 *et al.* 1982); trigeminal neuralgia (Law & Lilly 1995); temporomandibular disorder
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19 (Nixdorf *et al.* 2015), and headache (Alonso & Nixdorf 2006) are the most
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22 commonly reported.
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25 PDAP is a neuropathic pain condition due to underlying dysfunction of the
26
27 somatosensory system as a result of nerve damage (Baad-Hansen *et al.* 2013). All
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29 16 symptomatic cases with that demonstrated complete periapical healing at the first
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31 review in the present study fulfilled the PDAP diagnostic criteria (Nixdorf *et al.* 2012).
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34 All these patients had experienced continuous or recurrent pre-operative and
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36 persistent post-treatment symptoms lasting for more than 6 months, and located
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38 around the root-treated tooth without clinical and radiographic signs of pathosis.
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41 They also presented with other chronic pain problems including headache, TMD,
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43 neck, shoulder, or back pain.
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46 Spontaneous improvement or resolution of PDAP, as apparently found in the present
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48 study, has not previously been reported. Therefore, either the teeth in the present
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50 cohort should not be diagnosed with PDAP (but given with another label), or the
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52 criteria for PDAP should be modified to include account for the possibility of
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54 subsequent spontaneous resolution. Pigg *et al.* (2013) reported that one-third of
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56 patients diagnosed with "atypical odontalgia" perceived considerable improvement,
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and 10% became pain-free over a seven-year time-frame, after receiving various types of interventions. In the present study, despite the negative CBCT and clinical findings on teeth associated with symptoms, it may be speculated that periapical healing may actually have been incomplete at a microscopic/molecular level in a proportion of cases. This may account for spontaneous improvement in symptoms in these cases as healing then truly progressed to completion. Pain experience related to transition from the inflammatory to the proliferative phase of wound healing could be attributed to mediation through sensory neuropeptides. It is not implausible that contemporary diagnostic aids fail to detect tissue and molecular level inflammation, the undetected resolution of which may then abolish symptoms. (Brain 1997, Gunjigake *et al.* 2006) or sensory re-innervation of scars (Henderson *et al.* 2006). The s Spontaneous improvement may could also be related to attributed to patients' tolerance acceptance of the symptoms through a satisfying chronic pain after receiving satisfactory explanation (Pigg *et al.* 2013), or and development of coping strategies (Wolf *et al.* 2006), or attributable to their low intensity of their symptoms (Pigg *et al.* 2013). Pigg *et al.* (2013) reported that half of the patients diagnosed with "atypical odontalgia" were dissatisfied with their pain explanation at consultation. A larger proportion was, however, satisfied with the explanation amongst those showing symptom improvement compared to those not. The present study did not measure patients' satisfaction with their pain explanation but all those interviewed by phone 10 years later (in 2017) expressed satisfaction and contentment with the overall care received. Pigg *et al.* (2013) reported that low baseline pain intensity was a predictor of a favourable pain intervention outcome. The spontaneous improvement evident in this study may possibly reflect this phenomenon since a proportion had relatively low intensity symptoms.

The present study identified ~~five~~ ^{clinical} significant predictive factors ~~predicted for the~~ occurrence of symptoms associated with amongst root-treated teeth displaying periapical healing at review. They were: (1) history of systemic chronic pain; (2) pre-operative tooth pain; (3) ~~presence of~~ pre-operative tooth-crack; (4) teeth with pulps responsive ~~pulp to pulp tests~~; and (5) pre-operative size of periapical radiolucency. Two of the predictors (~~history of chronic pain disorder~~ [$P = 0.005$], and pre-treatment tooth pain [$P = 0.04$]); were ~~also~~ previously reported by Polycarpou *et al.* (2005). The present study, however, did not investigate the influence of duration of pre-treatment pain duration, which was found to be a significant predictor in other studies (Perkins & Kehlet 2000, Mattscheck *et al.* 2001, Nixdorf *et al.* 2016). The ~~history of chronic non-odontogenic pain and the presence of pre-operative pain~~ were found to have significant correlation with each other ($P < 0.0001$). It may be hypothesized that these two factors were ~~impossibly suggesting~~ a chain confounding relationship pathway; that patients suffering from chronic pain were more likely to experience pre-treatment tooth pain. Alternatively, pain development of pain may ~~have~~ be genetic susceptibility governed (Dominguez *et al.* 2008, Binkley *et al.* 2009, Dominguez *et al.* 2012).

~~found to be limited to the level above the canal orifice, without any associated periodontal probing defects. Persistent pain in the cases with cracks detected pre-operatively, coupled with complete periapical healing at the first review, might have been of periodontal origin as a result of tooth flexure under occlusal stress. This is supported by the observation that the symptoms resolved at the second review, by which stage they had been restored with full veneer cast restorations. Teeth with pulps responsive pulps to pulp tests diagnosed with irreversible pulpitis may trigger nociceptive signals nerve fibres at the root apex but such pain should theoretically~~

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resolve after root canal treatment unless. Such triggering, can however, initiate a deafferentation response was initiated in which the apical nerves become hypersensitive resulting in “atypical odontalgia” (Marbach 1996). That The size of the periapical lesion size was found to be a negative predictive factor. This finding is consistent with a previous study investigating prevalence of post-operative pain 2 days after root canal treatment (Ng *et al.* 2004), and explained by attributed to accommodation of any increased inflammatory pressure due to inflammatory exudate by the space afforded by incomplete periapical healing.

In summary, this study, showed that a considerable percentage (25%) of patients was still experiencing some form of post-operative sensation (perceived as either pain or discomfort) five to fourteen 5-14 months after following root canal treatment. This would undoubtedly pose uncertainty in the mind of both the dentist and patient about the treatment efficacy. Furthermore, it is likely to lead to delay in the placement of a cast restoration on a tooth with seemingly unexplained pain. Knowledge of the true prevalence of symptoms prolonged symptoms after (pain or discomfort) following root canal treatment would aid and thus appropriate management counselling at the time of treatment planning may help to smoothen the post-operative management of patient's expectations, particularly in the presence of identifiable predictive factors and anxieties. Equally, in the absence of such prior counselling, the ability to advise that persistent pain in a small proportion of patients is normal and would resolve spontaneously over time, is a valuable tool, in particular for those patients displaying the identified predictive factors. A clear explanation of the reasons for such sensations is crucial in enabling patients to cope with the discomfort and to avoid unnecessary intervention.

Conclusion

Persistent pain or discomfort associated with teeth showing periapical healing at first review after non-surgical root canal treatment decreased in intensity in most cases over the following 6-months. Longer-term follow-up showed spontaneous improvement or resolution of symptoms in the majority of those with confirmed absence of periapical disease. Five predictive factors (history of chronic pain problems, teeth responsive to pulp tests, teeth associated with pre-operative pain, ~~presence of tooth-crack~~ prior to treatment, and diameter of pre-operative radiolucency) were identified.

Figure legends

Figure 1. Flow chart outlining the clinical course of pain from teeth associated with evidence of healing from the first to the second review appointment.

Figure 2. Flow chart outlining the clinical course of discomfort from teeth associated with evidence of healing from the first to the second review appointment.

Table legends

Table 1. Criteria for periapical healing.

Table 21. Frequency distribution of pain or discomfort presenting at the first (n=264 teeth) and second (n=55 teeth) review appointments, stratified by various periapical healing outcomes.

Table 32. Intensity of pain (based on the SF-MPQ records) associated with teeth with periapical healing ("complete" or "incomplete") at the first review.

Table 3. Multi-variable logistic regression models incorporating presence of pain/discomfort as the binary dependent variable, and "history of chronic pain" (Model 1), or "pre-operative pain" (Model 2), and simultaneously with another three significant explanatory variables.

Appendix legends*Supplementary material - online only**Table S1*

Appendix I. Frequency distribution of choice of descriptors on the SF-MPQ at first review (n=260).

Table S2

Appendix II. Characteristics of patients experiencing persistent pain/discomfort associated with their root-treated tooth at the second review (11-20 months post-operatively), and their experience at 4 years (2011), and 10 years (2017) later.

Table S3

Appendix III. Single logistic regression models investigating the association between potential predictive factors and symptoms experienced at the first review (n = 249 teeth displaying evidence of periapical healing)